

Heart Rate Variability in Essential Hypertension Patients with Different Stages by Nonlinear Analysis: A Preliminary Study

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Abstract

Little is known about the nonlinear dynamics of heart rate variability (HRV) in hypertension patients with different stages. The aim of this study was to investigate the difference of HRV in hypertension patients by nonlinear methods. The patients with stage 2 hypertension (n=10) and stage 3 hypertension (n=12) were included in this study, in which the Allan factor (AF), approximate entropy (ApEn), Rényi entropy (REn), largest Lyapunov exponents (LLE) and wavelet-transform standard deviation (WTSD) as nonlinear characteristics of HRV were examined as well. The results showed that there are significant differences between stage 2 hypertension patients and stage 3 hypertension patients in parameters of AF, ApEn, REn and LLE. The present findings indicated that nonlinear parameters are sensitive to discriminate hypertension patients with different stages, and patients with stage 3 hypertension have depressed nonlinear behavior compared with patients with stage 2 hypertension. Duplicated research with larger samples is needed in the future work.

Key words

Nonlinear Analysis; Autonomic Nervous System; Hypertension

Introduction

Most population based studies confirm that hypertension profoundly increases an individual's risk of various cardiovascular consequences. Heart rate variability (HRV) has emerged as a practical, noninvasive tool to quantitatively investigate cardiac autonomic dysregulation in hypertension. HRV characterizes the variations in the intervals between consecutive heartbeats, that is, the variations in duration of R-R intervals between consecutive QRS complexes, measured by electrocardiograph (ECG). Assessment of HRV may provide quantitative information on the modulation of cardiac vagal and sympathetic nerve input. HRV analysis is a recognized tool for the estimation of cardiac autonomic modulations (Task Force 1996). Previous studies have

found that reduced HRV is a powerful and independent predictor of an adverse prognosis in patients with cardiovascular disease (Bauer et al. 2008, Huikuri and Stein 2012).

Numerous studies have assessed the relationship between hypertension and HRV (Garcia-Garcia et al. 2012, Schroeder et al. 2003, Singh et al. 1998, Terathongkum and Pickler 2004, Yoo et al. 2011). Linear methods, including time- and frequency-domain analysis, are applied in these studies. Actually, nonlinear phenomena involved in the genesis of HRV are determined by complex interactions of haemodynamic, electrophysiological and humoral variables, as well as by autonomic and central nervous regulations. It has been speculated that analysis of HRV based on the methods of nonlinear dynamics might elicit valuable information for the physiological interpretation of HRV and for the assessment of the risk of sudden death (Task Force 1996). Nonlinear dynamical HRV analysis, based on nonlinear mathematics and chaos theories, has been made so as to improve the understanding of the underlying physiological processes of the autonomous nervous system (Hoyer et al. 1997, Kim et al. 2005, Krstacic et al. 2012, Pivatelli et al. 2012). These methods do not attempt to assess the actual magnitude of HRV but to describe the complexity or fractal dynamics of the R-R interval time series. These methods may provide information beyond the conventional time and frequency domain methods (Makikallio et al. 1996, Voss et al. 1996).

In the present study, the nonlinear components of HRV were computed by using several methods, including Allan factor (AF), approximate entropy (ApEn), Rényi entropy (REn), largest Lyapunov exponents (LLE) and wavelet-transform standard deviation (WTSD). These methods differ from traditional methods, because they typically detect

qualitative rather than quantitative properties from HR time series. Also, these measures have been recognized by most researchers to examine the nonlinear characteristics of HRV (Ashkenazy et al. 1998, Beckers F. et al. 2001, Hagerman et al. 1996, Lake 2006, Turcott and Teich 1996). Most studies indicated that decreased nonlinear behaviour of heart rate is associated with pathological states.

To our knowledge, few studies have examined the nonlinear characteristic of HRV in patients with hypertension, and none investigated the differences between patients who were in different hypertension stages. The aim of this study was to investigate the HRV difference between essential hypertension patients with stage 2 hypertension and stage 3 hypertension by using nonlinear components of HRV.

Material and methods

Subjects

Essential hypertension patients were recruited in this study. 10 patients with stage 2 hypertension (SBP/DBP: 160-179/100-109) and 12 patients with stage 3 hypertension (SBP/DBP: $\geq 180/110$) were investigated. The information of the subjects is presented in Table 1. All subjects participating in this study gave written informed consent. The local Ethical Committee approved the protocol of the study.

TABLE 1 THE INFORMATION OF THE SUBJECTS.

	Stage 2 hypertension	Stage 3 hypertension
M/F	2/8	8/4
Age (year)	62.6 \pm 9.3 yr	68.6 \pm 7.3 yr
Height (cm)	162 \pm 5	166 \pm 4
SBP(mmHg)	171 \pm 10	193 \pm 7
DBP(mmHg)	105 \pm 8	125 \pm 9

Study Protocol

The ECG signals were collected while the patients were in a sitting position after resting for at least 20 minutes. The measurements were taken in the morning and at the same room by one trained research assistant according to a standardized method. 8 min ECG recordings were continuously collected (1,000 samples per second) using a Powerlab Acquisition System (ADInstruments Corporation, Sydney, Australia). Beat-to-beat cardiac interval values, i.e. heartbeat series, were automatically measured for each sinus beat and exported for further analysis.

There are many factors that may influence the HRV, including circadian rhythm, body position, activity level prior to recording, medication and breathing condition (Task Force 1996). For that reason, special

precautions were taken to maintain similar condition, such performing both recordings in the morning and in a sitting body position after an adaptation time of at least 15 minutes.

Nonlinear analysis of HRV

1) Allan Factor

The Allan factor is the ratio of the event-number Allan variance to twice the mean:

$$A(T) \equiv \frac{E\{[N_{i+1}(T) - N_i(T)]^2\}}{2E\{N_{i+1}(T)\}} \quad (1)$$

The Allan variance, as opposed to the ordinary variance, is defined in terms of the variability of successive counts (Turner et al. 1997, Turcott and Teich 1996).

2) Approximate Entropy

The approximate entropy, a measure of system complexity introduced by Pincus (Pincus S.M. 1991), has been widely applied in cardiovascular studies (Ho et al. 1997, Kim et al. 2005, Lin et al. 2001, Perkiomaki et al. 2002). Two parameters m and r must be chosen prior to the computation of approximate entropy, where m specifies the pattern length, and r is the effective filter. Here also, one has to compute the correlation integral $C^m(r)$ (with embedding dimension m and time lag 1). This measure is finally obtained as follows

$$ApEn(m, r, L) = \frac{1}{L-m} \sum_{i=1}^{L-m} \log C_i^{m+1}(r) - \frac{1}{L-m+1} \sum_{i=1}^{L-m+1} \log C_i^m(r) \quad (2)$$

Thus approximate entropy quantifies the (log) likelihood that sets of patterns that are close remain close on next incremental comparison. Smaller values of approximate entropy imply a greater likelihood that certain patterns of measurements will be followed by similar measurements. If the time series is highly irregular, the occurrence of similar patterns in the future is less likely. Higher values of approximate entropy indicate a more complex structure in the time series. For this study, m is set to be 2 and r is set to be 15% of the standard deviation of each time series. These values are selected on the basis of previous studies indicating good statistical validity for approximate entropy within these variable ranges (Pincus S. M. and Goldberger 1994).

3) Rényi Entropy

The Rényi entropy of order α , where $\alpha \geq 0$ and

$\alpha \neq 0$, is defined as

$$H_{\alpha}(X) = \frac{1}{1-\alpha} \log \left(\sum_{i=1}^n p_i^{\alpha} \right) \quad (3)$$

Here, X is a discrete random variable with possible outcome $1, 2, \dots, n$ and corresponding probabilities $p_i = \Pr(X = i)$ for $i=1, \dots, n$, and the logarithm is base 2. If the probabilities are $p_i = 1/n$ for all $i=1, \dots, n$, then all the Rényi entropies of the distribution are equal: $H_{\alpha}(X) = \log n$. In general, for all discrete random variables X , $H_{\alpha}(X)$ is a non-increasing function in α .

Applications often exploit the following relation between the Rényi entropy and the p-norm:

$$H_{\alpha}(X) = \frac{1}{1-\alpha} \log(\|X\|_{\alpha}). \quad (4)$$

Here, the discrete probability distribution X is interpreted as a vector in \mathbb{R}^n with $X_i = p_i \geq 0$ and $\sum_{i=1}^n X_i = 1$.

4) Largest Lyapunov Exponents

Lyapunov exponents represent the average exponential separation of initially nearby points. A positive Lyapunov exponent indicates that the initially neighboring trajectories diverge exponentially, which means that the system is sensitively dependent on initial conditions, the distinctive property of a chaotic system. An m -dimensional system has m Lyapunov exponents. Among those Lyapunov exponents, the largest Lyapunov exponent is enough to characterize the chaotic system in physiological applications (Radhakrishna et al. 2000). Our calculation is based on the algorithm developed by Rosenstein et al (Rosenstein et al. 1993), which is appropriate for small data sets.

5) Wavelet-Transform Standard Deviation

A dyadic discrete wavelet transform for the heartbeat sequence $\{\tau_i\}$ may be defined as:

$$W_{m,n}(m) = \frac{1}{\sqrt{m}} \sum_{i=0}^{L-1} \tau_i \psi(i/m - n) \quad (5)$$

A simple measure that can be derived from the wavelet transformation is the standard deviation of the wavelet transform as a function of scale:

$$\sigma_{\text{wav}}(m) = \left[E \left\{ W_{m,n}(m) - E[W_{m,n}(m)] \right\}^2 \right]^{\frac{1}{2}} \quad (6)$$

where the expectation is taken over the process of RR intervals, and is independent of n . It is readily shown that $E[W_{m,n}(m)] = 0$ for all values of m so that a simplified form for the wavelet-transform standard deviation emerges:

$$\sigma_{\text{wav}}(m) = \left\{ E \left[W_{m,n}(m)^2 \right] \right\}^{\frac{1}{2}} \quad (7)$$

Statistical Analysis

All available data were included in statistical analyses performed using the SPSS version 11 (Chicago, IL, USA). All data were presented as mean \pm standard deviation (SD) and 95% confidence interval (CI) for the mean. The significance of difference between groups was compared using one-way ANOVA followed by post-hoc analysis. P less than 0.05 was considered statistically significant.

Results

Table 2 shows the comparison of nonlinear parameters between patients with stage 2 hypertension and stage 3 hypertension. The values of mean \pm SD and 95% CI for the mean in nonlinear parameters are presented. Compared to patients with stage 2 hypertension, patients with stage 3 hypertension have smaller value of mean \pm SD and lower 95% CI for the mean for all nonlinear parameters. Specifically, in stage 3 hypertension patients, parameters of AF significantly decreased ($P=0.010$), as well as ApEn ($P=0.008$), REN ($P=0.006$), and LLE ($P=0.013$). No significant differences were found for parameters of WTSD between patients with stage 2 hypertension and stage 3 hypertension ($P>0.05$).

TABLE 2 COMPARISON BETWEEN PATIENTS WITH STAGE 2 HYPERTENSION AND STAGE 3 HYPERTENSION. VALUES ARE 95% CI FOR THE MEAN

	Stage 2 hypertension (n=10)		Stage 3 hypertension (n=12)		P
	Mean \pm standard deviation	95% CI	mean \pm standard deviation	95% CI	
AF	0.039 \pm 0.062	0.027- 0.051	0.022 \pm 0.013	0.013- 0.029	0.010
ApEn	1.64 \pm 0.62	1.071- 2.21	0.803 \pm 0.324	0.63- 1.13	0.008
REn	2.11 \pm 0.563	1.70-2.51	1.39 \pm 0.43	1.13- 1.72	0.006
LLE	0.134 \pm 0.042	0.09- 0.15	0.082 \pm 0.039	0.05- 0.10	0.013
WTSD	32.6 \pm 19.7	16.4-48.9	26.6 \pm 17.1	9.8- 38.5	ns

AF: Allan factor; ApEn: Approximate entropy; REn: Rényi entropy; LLE: Largest Lyapunov Exponents; WTSD: Wavelet-Transform Standard

Deviation

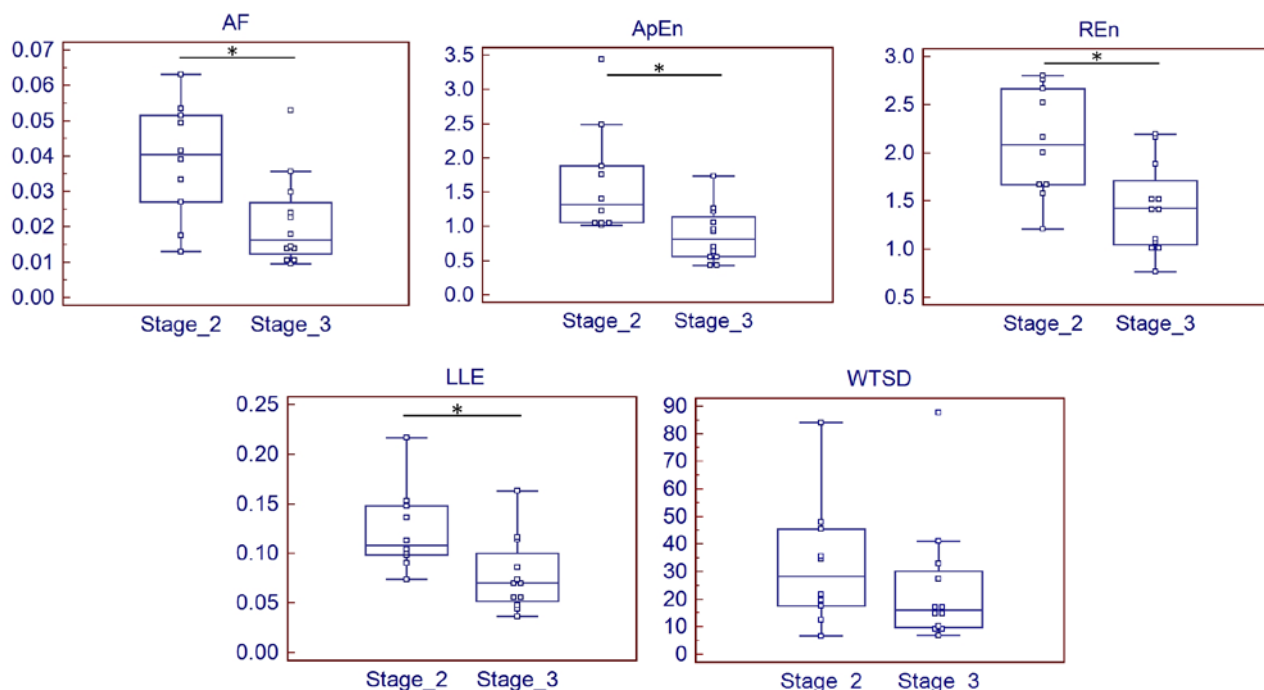


FIG. 1 DISTRIBUTION OF VALUES FOR NONLINEAR PARAMETERS IN PATIENTS WITH STAGE 2 AND STAGE 3 HYPERTENSION. THE SIGNIFICANT DIFFERENCES ($P < 0.05$) WERE MARKED WITH “*”

In Fig. 1, the values of nonlinear parameters are presented, and box-and-whisker plots are applied to present the median and the values from the lower to upper quartile (25 to 75 percentile). Patients with stage 3 hypertension have lower values in parameters of AF, ApEn, REn and LLE (all $P < 0.05$) compared to patients with stage 2 hypertension. No statistically significant differences were found in parameters of WTSD between groups.

Discussion

Fluctuations in the heartbeats series represent the heart's ability to respond to naturally occurring physiologic variations in cardiovascular activity and regulatory impulses from various cardiovascular control systems. When the research focus is on dynamic changes of autonomic tone and/or prediction of subsequent physiologic outcome, HRV is preferred over heart rate as an index of autonomic cardiac response. It is recognized that heartbeats fluctuations stem from dynamics of chaotic nature and exhibit short range correlation governed by deterministic laws. In addition, the predictive value including the time and frequency domain measures of HRV, is relatively low in some studies for risk stratification (Odemuyiwa et al. 1991, Redwood et al. 1997). In order to get a better understanding of heart rate regulation, methods based on nonlinear mathematics and chaos theories for risk stratification in clinical practice are necessary and

required. Altered heart rate dynamics has been demonstrated in patients with chronic heart failure (Ho et al. 1997) myocardial infarction (Makikallio et al. 1996) and a propensity for ventricular arrhythmias (Makikallio et al. 1999). No studies investigate the changes of heart rate dynamics in Essential Hypertension Patients.

AF is a useful measure of HRV (Turcott and Teich 1996). An excess above unity reveals that a sequence is less ordered than a homogeneous Poisson point process, while values below unity signify sequences which are more ordered. The lower AF in patients with stage 3 hypertension demonstrated the higher ordered heartbeats series, indicating the reduced HRV.

ApEn and REn quantify the entropy of the system (Pincus S.M. 1991, Lake 2006). Entropy measures the degree to which the occurrence of a value depends on its predecessors in the input. The more regular and predictable the heartbeats series is, the lower the value of the entropy will be. On the other hand, a more random heartbeats series will lead to higher entropy values. Generally, healthy person have higher values of entropy compared to patients with impaired cardiovascular system (Makikallio et al. 2000). ApEn is an index of overall complexity and predictability of heart beat series. REn, which is the measures of heart rate gaussianity, was utilized to enhance and complement the analysis of biological signals using ApEn (Lake 2006). The Gaussianity of heartbeats series

is a measure that can be linked to physiological complexity. Lower ApEn and REn were observed in patients with stage 3 hypertension compared with patients with stage 2 hypertension, indicating that the more severe hypertension lowered the complexity of heartbeats series. Previous studies showed that heart diseases presented changes in the complexity of heartbeats series, assessed by ApEn. Vikman et al. (Vikman et al. 1999) revealed reduced ApEn preceding spontaneous onset of paroxysmal atrial fibrillation in patients without structural heart disease. ApEn is mostly linked with vagal modulation (Beckers F. et al. 2001). The present findings suggested the reduced vagal nervous activity in patients with stage 3 hypertension.

The LLE quantifies the sensitivity of the system to initial conditions. This is characterized by the average rate of divergence of two neighboring trajectories in phase space and gives a measure of predictability. A negative value implies that the orbits approach a common fixed point. A positive value can be taken as a definition of chaos provided that the system is known to be deterministic (Rosenstein et al. 1993). Larger values of the LLE indicate more complex behavior. The smaller LLE in patients with stage 3 hypertension indicated the reduced HRV compared to the patients with stage 2 hypertension, suggesting the more severe impairment of autonomic nervous system in patients with stage 3 hypertension. However, in previous studies, this index was reported to be uncorrelated to autonomic modulation (Hagerman et al. 1996).

WTSD has recently been shown to be quite valuable for HRV analysis (Ashkenazy et al. 1998, Thuner et al. 1998). The depression of WTSD is likely associated with the impairment of autonomic nervous system function. Although no significant differences were found between two groups in the present study, the patients with stage 3 hypertension did have a lower value of WTSD, indicating the reduced baroreflex sensitivity.

Limitations

Despite promising results in this study, there are some limitations to consider. First, this study was performed with small populations. Even nonlinear heart rate dynamic seem to be potential tools for risk stratification in hypertension patients, replication research with larger samples is needed to confirm the present findings. Second, several factors limit the clinical utility of nonlinear HRV analysis. Physiological

factors, such as sex (Goldberger et al. 2002) and ageing (Beckers F. et al. 2006), have been shown to influence nonlinear heart rate dynamics. Although the two groups did not differ significantly in age and body weight, the difference of gender distribution in this preliminary study prompted the future investigation regarding gender difference when altered heart rate dynamics is interpreted.

Conclusion

In recent years, new dynamic methods of HRV quantification have been used to uncover nonlinear fluctuations in heart rate that are otherwise not apparent. The nonlinear variations would enable the cardiovascular system to respond more quickly to changing conditions. This study has investigated the nonlinear characteristics of HRV in patients with stage 2 and stage 3 hypertension. Patients with stage 3 hypertension have depressed nonlinear behavior of heartbeat series compared with those with stage 2 hypertension. This can be related to the general concept of decreasing autonomic modulation due to high blood pressure.

Although methods derived from nonlinear dynamics have been successfully applied to many scientific disciplines, the physiological background underlying nonlinear heart rate dynamics is far from being fully understood. Therefore, better understanding of the physiology of altered heart rate dynamics is required before these methods will gain any significant position in clinical practice.

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